REMARKS

This responds to the Final Office Action dated July 27, 2011 and Advisory Action date October 6, 2011.

Claims 7 and 10 are amended, claims 1-6 and 13-15 are withdrawn, claims 11-12 are cancelled, no claims are added; as a result, claims 1-10 and 13-15 are pending in this application.

Applicants thank the Examiner for noting the typographical errors in claims 7 and 10. The amendments to claims 7 and 10 render the objection of the claims moot. Thus, Applicants respectfully request withdrawal of the objection.

The Rejection of Claims Under § 112

Claims 7-9 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking an adequate written description in the specification. Specifically, the Office Action contends that the instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Applicants respectfully disagree with and traverse this rejection. The written description requirement of 35 U.S.C. § 112, first paragraph, is met "if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an [applicant] had possession of the concept of what is claimed." *Ex parte Parks*, 30 U.S.P.Q.2d 1234, 1236 (Bd. Pat. App. Int. 1994). Furthermore, "[t]he absence of definitions or details for well-established terms or procedures should not be the basis for a rejection for lack of written description." *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. The Examiner must establish a *prima facie* case under § 112 ¶ 1 by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. Applicant's description as filed is presumed to be adequate, unless or until the Examiner presents a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a

description of the invention defined by the claims. See, e.g., *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976), and *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

Applicant respectfully submits that the Examiner has not established a *prima facie* case under § 112 ¶ 1 and there is no evidence why one skilled in the art would not recognize that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. In fact, the opposite is true, as discussed previously and hereinbelow. Applicant respectfully submits that the instant application clearly meets the requirements for written description.

Claim 7 currently recites "a method for inducing cytostasis comprising administering to a patient in need thereof a therapeutically effective amount of T type calcium channel selective inhibitor so as to induce cytostasis in said patient." Support for claim 7 can be found in paragraph [0005] of the published application (Pub. No. 2008/0160009), which states the library of compounds that the present invention has developed can act cytostatically. Clearly, mibefradil is a compound of the present invention and is specifically referred to in the very next paragraph [0006] (noting that it is selective for the T-type channel as opposed to the L-type channel). See also paragraphs [0051] in which it is stated that mibefradil is a well known T type voltage gated calcium channel blocker, it has been shown that blockade of voltage gated calcium in cancerous, electrically non-excitable cells, which constitute solid tumors, inhibits proliferation (see 6,413,967), and, as demonstrated by the instant application, mibefradil inhibits proliferation of electrically non-excitable cancer cells by inhibiting calcium entry into them (FIGS. 1A-1F).

Paragraphs [0020], [0072] and [0073] and FIGS. 1A-1F of the present application teach that mibefradil can inhibit calcium entry in several cancer cell lines with concordant inhibition of proliferation. It is well known by one of skill in the art that inhibition of calcium entry can reversibly inhibit cell growth.[1] As one of skill in the art would readily appreciate, reversible inhibition of cell growth is consistent with cytostasis rather than cytotoxicity. Such an inference would be made because preferred cytotoxic agents serve not in a reversible manner, but instead

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[1] Whitfield JF, Boynton AL, MacManus JP, Sikorska M, Tsang BK. (1979) The regulation of cell proliferation by calcium and cyclic AMP. *Mol Cell Biochem*, 27, 155-179; Veigl ML, Sedwick WD, Vanaman TC. (1982) Calmodulin and Ca^{2+} in normal and transformed cells. *Federation Proceedings*, 82, 2283-2288.

act to induce cell death.[2] Therefore, one of skill in the art in possession of the present specification would clearly understand that the figures and examples provided therein were aimed not at inducing cell death (cytotoxic), but were describing reversible inhibition of cell growth, namely cytostasis, as presently recited in the claims.

Consequently, one of ordinary skill in the art would readily understand that the originally-filed specification, read in view of knowledge available to the art, satisfies the written description requirement, and therefore, that Applicant had possession of the claimed invention as of the filing date of the application. Thus, reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 7-9 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Office Action contends that the instant specification does not contain subject matter which is described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Office Action states "[o]ne of skill in the art cannot extrapolate the teachings of the specification to enable the claims because the claims are drawn to a method for inducing cytostasis comprising administering to a patient in need thereof a therapeutically effective amount of mibefradil so as to induce cytostasis in said patient; however, the specification has only presented data showing that mibefradil inhibits proliferation of prostate cancer cell lines *in vitro;* the specification presents no examples to demonstrate that mibefradil can induce cytostasis in cells or in a patient."

The Applicants respectfully disagree with and traverse this rejection. The Applicants respectfully submit that the specification adequately complies with the enablement requirement as follows.

As discussed above, claim 7 currently recites, among other things, "a method for inducing cytostasis…so as to induce cytostasis in said patient." For adequate enabling support the Applicants point to the teachings of paragraph [0005], which states the library of compounds that the present invention has developed can act cytostatically and, paragraphs [0020]. [0051], [0072] and [0073] and FIGS. 1A-1F, which teach that mibefradil blocked the calcium entry from

[2]Blagosklonny MV (2005) Carcinogenesis, cancer therapy and chemoprevention. *Cell Death Differ*, 12, 592-602.

the extracellular medium that is necessary for cancer cell division and proliferation. Thus, the figures and examples provided therein were aimed not at inducing cell death (cytotoxic), but were describing reversible inhibition of cell growth, namely cytostasis, as presently recited in the claims.

First, the MPEP explicitly states that the question of compliance with the enablement requirement of 35 U.S.C. 112 first paragraph, "does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic.'"[3] The MPEP further explains that a working example can be based upon work performed, whereas a prophetic example describes an embodiment based on predicted results rather that the results actually obtained. All that is required is that there must be a correlation between the example contained in the specification and the claim. In fact, the Federal Circuit has reversed PTO decisions based on the erroneous finding that *in vitro* data did not support *in vivo* applications.[4]

Second, the MPEP explicitly states that because "the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model."[5] The Office Action states that "the claims are drawn to a method for inducing cytostasis comprising administering to a patient in need thereof a therapeutically effective amount of mibefradil so as to induce cytostasis in said patient; however, the specification has only presented data showing that mibefradil inhibits proliferation of prostate cancer cell lines *in vitro*." As such, Applicants respectfully assert that the instant 35 U.S.C. § 112, first paragraph rejection is improper because the Office Action has failed to give reasons for a conclusion of lack of correlation between the *in vitro* data and an *in vivo*.

"An in vitro or in vivo animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention... if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against

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[3] U.S. PAT. & TRADEMARK OFFICE, U.S. DEP'T OF COMMERCE, MANUAL OF PATENT EXAMINING PROCEDURE § 2164.02 (8th ed., 2nd rev. 2004) [hereinafter MPEP].
[4] *See In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).
[5] MPEP § 2164.02.

correlation and decide whether one skilled in the art would accept the model as ***reasonably correlating to the condition.***" See, MPEP 2164.02.

Applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, **all that is required is a reasonable correlation between the activity and the asserted use**. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).

Applicant submits that there is a reasonable correlation between the instant claims and the *in vitro* data described in the specification and shown in the Figures.

Finally, the MPEP states that a specification need not contain a working example if the invention is disclosed in a manner such that one skilled in the art will be able to practice it without an undue amount of experimentation.[6] It is well settled law that at times, even when the amount of experimentation required to practice the scope of the claimed invention might have been extensive, the experimentation is still routine if the necessary techniques are well known to those skilled in the art.[7] In the specific instance of mibefradil, it is well known in the art that certain doses are recommended for administration to a patient in need thereof.[8] As such, the Applicants respectfully assert that although one of skill in the art in possession of the present disclosure may need to perform routine experimentation to obtain the appropriate dose of mibefradil for therapeutic effect in a patient, such routine experimentation is not extensive, and does not rise to the level of impermissible undue experimentation.

Claims 8 and 9 are dependent upon claim 7. Accordingly, claims 8 and 9 incorporate the limitations of claim 7. As such Applicants respectfully submit that the features of claims 7-9 are enabled and comply with 112(1). Thus, Applicants respectfully request withdrawal of this rejection.

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[6] Id.; *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).
[7] *Ex parte* Kubin, Appeal 2004-0819, 2007 WL 2070495 (B.P.A.I. May 31, 2007).
[8] Welker HA (1998) Single- and multiple-dose mibefradil pharmacokinetics in normal and hypertensive subjects. *J Pharm Pharmacol*, 50, 983-7.

The Rejection of Claims Under § 103

Claim 10 remains rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Bertolesi et al. (Mol. Pharmacol. 62:210-219, 2002, hereafter Bertolesi) in view of Gray et al. (U.S. Patent Number 6413967, hereafter '967).

Applicants respectfully traverse the rejections and request reconsideration and withdrawal of the rejection.

The U.S. Supreme Court's decision of *KSR v. Teleflex*[9] provided a multi-prong test to evaluate obviousness. This multi-prong test set forth a list of requirements to support a conclusion of obviousness, including—among other things—a finding that all the claimed elements were known in the prior art.[10] Applicants maintain that the limitation of inducing cytostasis in a patient, as claimed in currently amended claim 10, is not disclosed in the cited art.

Applicants cannot find in the cited portions of Bertolesi, Gray or the Office Action's reasoning a disclosure of inducing cytostasis in a patient. In fact, Bertolesi appears to expressly teach away from this. Bertolesi explicitly rejects the hypothesis that T type calcium blockers inhibit proliferation by cell cycle arrest and cytostasis (page 214 section beginning in left column titled "Cytostatic **or** Cytotoxic Effects of Pimoxzide and Mibefradil") (emphasis added). Bertolesi interprets the results to indicate that these drugs block proliferation by inducing cell death. Conversely, the major premise of the presently claimed invention is that cytostasis is induced by inhibition by T type calcium blockers and thereby inducing a cell cycle blockade. As previously pointed out by the Applicants, cytostatic and cytotoxic mechanisms are fundamentally inapposite. For example, cytotoxic drugs cause collateral damage to normal, healthy tissues, which bring dose and schedule limiting toxicities. On the other hand, cytostatic drugs can be administered to patients chronically. As implicitly acknowledged by Bertolesi by investigating cytostatic or cytotoxic effects rather than cytostatic and cytotoxic effects, cytotoxicity and cytostasis is mutually exclusive. In sum, Applicants respectfully submit that Bertolesi not only fails to disclose or suggest inducing cytostasis, Bertolesi actually teaches away from the subject matter of claim 10, as currently amended.

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[9] *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).
[10] *See also*, Manual of Patent Examining Procedure §§ 706.02(j), 2143(A) (2008); MPEP § 2142 (2006) (citing *In re Vaeck*, 947 F.2d, 488 (Fed. Cir. 1991)). Cited approvingly in *Ex parte Wen Wen* and Patricia NG at 7; Appeal No. 2009-000776; decided September 25, 2009.

The Applicant respectfully asserts that Gray also fails to disclose or suggest inducing cytostasis or inducing cytostasis in a patient. As such, the Applicants assert that Gray does not remedy the deficiencies of Bertolesi.

As the 35 USC § 103 rejection of the Office Action has been obviated by the amendments to independent claim 10, claim 10 is presently believed to be in allowable condition. Reconsideration and withdrawal of the rejection of claim 10 is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6905 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

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